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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
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| 09/155,023 | 09/21/98 | GUILE S | 2257-137 |

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| EXAMINER | |
|---|---|
| MCKENZIE, T | |
| **ART UNIT** | **PAPER NUMBER** |
| 1624 | |

**DATE MAILED:** 03/29/00

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

| Office Action Summary | Application No. 09/155,023 | Applicant(s) GUILE ET AL. | |
|---|---|---|---|
| | Examiner Thomas McKenzie Ph. D. | Art Unit 1624 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

**Status**

1)☒ Responsive to communication(s) filed on *21 September 1998* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,10,13 and 14* is/are rejected.

7)☒ Claim(s) *3-9,11 and 12* is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☒ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☒ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

**Attachment(s)**

14) ☒ Notice of References Cited (PTO-892)
15) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
16) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
17) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
18) ☐ Notice of Informal Patent Application (PTO-152)
19) ☐ Other: .

## DETAILED ACTION

1. This action is in response to an application filed on 9/21/98. There are fourteen claims. Claims 1-8 and 10-12 are compound claims, claim 9 is a composition claim, claim 13 is a use claim, and claim 14 is a process claim. An office action dated 9/28/99 has been withdrawn. This is the first action on the merits.

### *Priority*

2. The specification is objected to because it needs to state that the application is filed under rule 371. An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78). Examiner suggests "This application is the National Stage Application of PCT/SE98/01393, which claims priority from Swedish application 9702773-4 filed July 22, 1997.

### *Oath/Declaration*

3. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02. The oath or declaration is defective because the full name of each inventor (family name and at

least one given name together with any initial) has not been set forth. The first names of all the inventors are not present in their signatures. See MPEP 605.04(b). The fourth edition of the MPEP (revised 10/81) says on page 84.1 "unless a statement has been filed over the applicants own signature setting forth that his or her name as signed contains at least one given name without abbreviation..."

***Abstract***

4. Applicant is reminded of the proper content of an abstract of the disclosure. A patent abstract is a concise statement of the technical disclosure of the patent and should include that which is new in the art to which the invention pertains. In chemical patent abstracts for compounds or compositions, the general nature of the compound or composition should be given as well as its use, *e.g.*, "The compounds are of the class of alkyl benzene sulfonyl ureas, useful as oral anti-diabetics." For processes, the type reaction, reagents and process conditions should be stated, generally illustrated by a single example unless variations are necessary. The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 250 words. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for

consulting the full patent text for details. The language should be clear and concise and should not repeat information given in the title. Avoid the form and legal phraseology often used in patent claims, such as "means" and "said". Avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc. The abstract is too short and generic. Examiner suggests claim 2, including the figure Ia, the synthesis, and the utility.

***Title***

5. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The examiner suggests "1,2,3-Triazolo[4,5-d]pyrimidines as $P_{2T}$-receptor antagonists".

***Claim Objections***

6. Claim 8 is objected to because of the following informalities: line 27 on page 130 is missing a bracket, line 31 on page 131 "phenoyphenyl", line 7 on page 136 "N,N-Dimethylphenyl", and line 35 on page 137 is missing a parenthesis. Appropriate correction is required.

7. Claims 10-12 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to limit further the subject matter of a previous claim.

Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The phrases "for use in therapy" in claim 10, "for use in the treatment .... " in claim 11 and "for use in the treatment .... " in claim 12 are statements of intent. These are purely mental steps, which do not provide any structural limitations. Hence, claims 10-12 have the identical scope to claim 1.

8. Claim 13 is objected to because of the following informalities: there is a missing "of" between "treatment" and "a" in the first line of this claim. Appropriate correction is required.

***Claim Rejections - 35 USC § 112***

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for 1,3-benzodioxole compounds as a possible $R^2$ group, does not reasonably provide enablement for any "fused 5- or 6- membered saturated ring containing one or two oxygen atoms". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly

connected, to make the invention commensurate in scope with these claims. In the specification, in examples 56 and 57 on pages 64-65, applicants teach how to make 1,3-benzodioxole compounds. They do not teach how to make other "fused 5- or 6- membered saturated ring containing one or two oxygen atoms", for example 1,4 benzodioxane or 1,2-benzodioxole compounds.

10. Claim 1 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for "acyl, alkyl sulfonyl" of finite length, "aryl", and "arylsulfonyl or arylcarbonyl" with a limited number of carbon atoms, does not reasonably provide enablement for alkyl groups of infinite length or aromatic groups with an unlimited number of rings. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. In line 5 of page 127 the length of the alkyl groups associated with "acyl, alkyl sulfonyl" is not specified. In the last line on page 126 the size of "aryl" and the length of the carbon chain associated with "acyl" is not specified. The Board of Patent Appeals and Interferences held, and the court affirmed *In re Hawkins* 179 USPQ 157 that "We agree with the examiner that the broad limitations to "aryl" in claims 2, 4, and 8, "alkyl" in claims 8, 17, 40, 41, 42, 44, 45, 56 to 61, and 65, .....

are not supported in their scope by the specification. The "aryl" groups could be multiple rings, counting as many as twenty or more. Clearly, this breadth is not shown to be supported by the original disclosure. Compounds having such complex configurations would not be expected to have even the imprecisely disclosed utility ... . The same is true of the claimed "alkyl" radicals which may have unlimited chain lengths. ..... We find that the specification does not suggest by way of examples or otherwise that appellant believed all "aryl," "alkyl," and "aliphatic" groups would be operable in face of the substantial indications to one of ordinary skill in the art to the contrary."

11. Claim 14 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants are by no means enabled for the reactions implied by the penultimate line on page 139. For example, do applicants posses a reaction capable of converting a phenyl group into a nitro group, and where in the specification is such a reaction described? Note that the claim sets forth any functional group to be converted to any other functional group.

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim language in lines 15 and 16 of page 126 may be read in several ways. Is a "fused 5- or 6- membered saturated ring containing one or two oxygen atoms", a candidate for $R^2$ or a substituent on alkyl or phenyl of line 14. Is "phenyl" in line 16 a second recitation of this possibility for $R^2$ or a substituent on alkyl or phenyl of line 14?

13. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The "fused 5- or 6- membered saturated ring containing one or two oxygen atoms" language is confusing. Fused to what? Is only the oxygen-containing ring saturated or must any ring to which it is fused also be saturated? If it is intended to be fused to an alkyl group, what is the structure of such a molecule? What are the other atoms forming the "fused 5- or 6-membered saturated ring containing one or two oxygen atoms"? The Board of Patent Appeals and Interferences held, and the court affirmed *In re Hawkins* 179 USPQ 421 that "It must also be noted that the claim terminology is so broad that it

does not even require that the heterocyclic group contain a carbon atom. Heterocyclic ring systems containing phosphorus, boron, silicon, and other elements in addition to nitrogen and oxygen without the inclusion of carbon atoms are well-known and could not be expected to produce compounds having the properties herein claimed."

14. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In line 7 on page 126, "$C_{2-6}$alkenyl" is claimed twice. If applicants intend to amend the second recitation of this claim, they must illustrate that no new matter is being presented.

15. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In the last line on page 126 and in the fifth line on page 127, the word "acyl" is used. The accepted meaning of the term "acyl" is "any acid substituent with the OH group removed". The term acyl is indefinite. Does this embrace the acids of sulfur and phosphorus? How is the acyl group attached? Is it through the central atom of the acid group or through some other carbon atom? What is the specific stem, i. e. if acyl is RC(O), what is R?

16. Claim 2 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 2 is an independent claim, yet definitions of R and $R^1$-$R^4$ are not provided.

17. Claim 4 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 4 recites the limitation "$C_{3-8}$alkyl" in line 19, page 127. There is insufficient antecedent basis for this limitation in the claim. In claim 1, in line 13 the limitation "$C_{1-6}$alkyl" is claimed as a possible substituent on $R^2$.

18. Claim 10 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The word "therapy" is indefinite for we do not what "therapy" is intended. Do applicants think their compounds will be useful in physical therapy, shock therapy, or hydrotherapy for example?

19. Claim 13 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim provides for the use of

claimed compounds, but the claim does not set forth any steps involved in determining which are the "platelet aggregation disorder [s]". It is unclear which diseases are "platelet aggregation disorder [s]". There are dozens of such disorders including ticlopidine-induced aplastic anemia, lymphocytic colitis, Glanzmann's thrombasthenia, erythromelalgia, thrombotic thrombocytopenic purpura, pulmonary hypertension, atherosclerosis, von Willebrand disease, essential thrombocythemia during pregnancy, heparin-induced thrombocytopenia, pre-eclampsia, Bernard-Soulier syndrome, hyperleukocytic syndrome, myeloproliferative disorders, stroke, migraine, and Hermansky-Pudlak syndrome amoung others. Determining whether a given disease responds or does not respond to such a $P_{2T}$-receptor antagonist will involve undue experimentation. Suppose that a given drug, which has receptor antagonist properties *in vitro*, when administered to a patient with a certain disease, does not produce a favorable response. One can not conclude that specific disease does not fall within this claim. Keep in mind that:

A. It may be that the next patient will respond. No pharmaceutical has 100% efficacy. What success rate is required to conclude our drug is a treatment? Thus, how many patients need to be treated? If "successful treatment" is what is

intended, what criterion is to be used? If one person in 10 responds to a given drug, does that mean that the disease is treatable? One in 100? 1,000? 10,000? Will the standard vary depending on the current therapy for the disease?

B. It may be that the wrong dosage or dosage regimen was employed. Drugs with similar chemical structures can have markedly different pharmacokinetics and metabolic fates. It is quite common for pharmaceuticals to work and or be safe at one dosage, but not at another that is significantly higher or lower. Furthermore, the dosage regimen may be vital --- should the drug be given e.g. once a day, or four times in divided dosages? The optimum route of administration can not be predicted in advance. Should our drug be given as a bolus *iv* or in a time release *po* formulation. Thus, how many dosages and dosage regimens must be tried before one is certain that our drug is not a treatment for this specific disease?

C. It may be that our specific drug, while active *in vitro*, simply is not potent enough or produces such low concentrations in the blood that it is not an effective treatment of the specific disease. Perhaps a structurally related drug is potent enough or produces high enough blood concentrations to treat the disease in question, so that the first drug really does fall within the claim. Thus, how many

different structurally related receptor antagonists must be tried before one concludes that a specific compound does not fall within the claim?

D. Conversely, if the disease responds to our second drug but not to the first, both of whom are receptor antagonists *in vitro*, can one really conclude that the disease falls within the claim? It may be that the first compound result is giving the accurate answer, and that the success of second compound arises from some other unknown property which the second drug is capable. It is common for a drug, particularly in the CNS, to work by many mechanisms. The history of psychopharmacology is filled with drugs, which were claimed to be a pure receptor XYX agonist or antagonist, but upon further experimentation shown to effect a variety of biological targets. In fact, the development of a drug for a specific disease and the determination of its biological site of action usually precede linking that site of action with the disease. Thus, when mixed results are obtained, how many more drugs need be tested?

E. Suppose that our drug is an effective treatment of the disease of interest, but only when combined with some totally different drug. There are for example, agents in antiviral and anticancer chemotherapy which are not themselves

effective, but are effective treatments when the agents are combined with something else.

Consequently, determining the true scope of the claim will involve extensive and potentially inconclusive research. Without it, one skilled in the art cannot determine the actual scope of the claim. Hence, the claim is indefinite.

20. Claim 14 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 14 is an independent claim, yet definitions of R and $R^1$-$R^4$ are not provided.

21. Claim 14 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "protected derivatives" in lines 1, 6, 11, and 18 is indefinite. Derivatives of what and protected against what?

***Allowable Subject Matter***

22. Claims 3-9 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Compounds are patenable over Cox ('496). The compounds described in Cox have the group R at

a higher oxidation state then claimed in the current application. Compounds are patenable over Bonnert (WO 98/28300). The compounds described in Bonnert have the group R at a higher oxidation state then claimed in the current application.

***Conclusion***

23. Please direct any inquiry concerning this communication or earlier communications from the examiner to Thomas C. McKenzie, Ph. D. whose telephone number is (703) 308-9806. The examiner can normally be reached on 8:30 to 5:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mukund J. Shah can be reached on (703) 308-4716. The fax number for the organization where this application is assigned is (703) 308-4556 for regular communications. Please direct any inquiry of a general nature or relating to the status of this application to the receptionist whose telephone number is (703) 308-1235.

TCMcK
March 23, 2000

RICHARD L. RAYMOND
PRIMARY EXAMINER
ART UNIT 1614